96. (New) The method of claim 76, wherein X_1X_2 are GpA and X_3X_4 are both pyrimidines.

97. (New) The method of claim 76, wherein the oligonucleotide is 8 to 40 nucleotides in length.

98. (New) The method of claim 71, wherein 5' X_1 X_2CGX_3 X_4 3' is not palindromic.

REMARKS

Applicants have amended the specification to correct typographical error in a sequence referred to as ODN 1585 (SEQ ID No. 12). The sequence appeared in its correct form in the sequence listing. Nucleotide no. 15 of SEQ ID No. 12 appears on page 22 of the specification as C rather than a G. This error was typographical in nature and correction of it does not constitute new matter.

Substitute sheets for page 38 and page 47 have also been submitted herewith. It was noted in the Office Action (paper no. 9, page 2) that informalities were found on page 38 and page 47 in which two lines were illegible. Applicants have corrected there informalities by submitting substitute sheets. On page 38, the last line (following the line beginning with "1842") has been rewritten in a legible form. No other changes were made to the text on page 38. On page 47, the fourth line after the table was rewritten in a legible form. No other changes were made to page 47. No new matter is added by these corrections.

Claim 1 has been cancelled and is no longer being pursued in the above-identified patent application. Claim 1 was maintained only for the purpose of keeping a claim pending at all times in the divisional application. Claims 57 and 58 have been amended to change the language "end of the nucleic acid" to "inter-nucleotide linkages". The amendment does not narrow the scope of the claims. It serves only to clarify that the phosphate backbone modification is occurring within the inter-nucleotide linkages at the 5' or 3' end of the nucleic acid. The phosphate backbone modification could not occur at places other than the inter-

nucleotide linkages. Claim 72 has been amended to correct a typographical error. The "0" was removed from the word "modification". The amendment does not alter the scope of the claim. Claim 71 has also been amended to remove the limitation "and wherein the sequence is not palindromic". This limitation was incorporated into new dependent claim 98. Applicants have amended the claim to remove this limitation because the claim is too narrow in scope as written. The original claim 71 should have been filed without this limitation. The prior art relating to palindromic oligonucleotides does not show that these oligonucleotides can enhance ADCC. Thus, the prior art would not have combined a palindromic oligonucleotide with an antibody for the treatment of cancer in order to enhance ADCC.

New claims 76-98 have been added. New claim 76 relates to a method for treating or preventing cancer by administering to a subject an immunostimulatory CpG containing oligonucleotide, wherein the CpG sequence is not palindromic. Support for the limitation that the oligonucleotides are useful for treating or preventing cancer is found throughout the specification but at least in the summary of the invention on page 9, lines 5-8 and in the detailed description of the invention on page 13, line 33 - page 14, line 4 and page 53, lines 5-11. New dependent claims 77-97 have a similar scope to pending claims 43-63. New claim 98 depends from claim 71 and adds the limitation that the sequence is not palindromic. No new matter has been added by the claim amendments or additions.

References

Applicants submit herewith copies of references which were previously cited on form PTO-1449 and which were not considered because copies could not be identified in the parent files. It is indicated in the Office Action (paper no. 9) that Applicants could submit copies of the indicated references in response to the Office Action without the submission of any fee for such consideration.

Rejection of Claims 42-75 Under 35 U.S.C. §112, Second Paragraph

Claims 42-75 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite because of some of the claim language.

In particular, claims 57 and 58 have been rejected because of the phrase phosphate backbone modification of the 5' or 3' end of the nucleic acid. Applicants have amended claims 57 and 58 to clarify that the phosphate backbone modification occurs in the inter-nucleotide linkages between bases at the 5' or 3' end of the molecule. The original language used in the claims was intended to cover the phosphate backbone modification occurring within the inter-nucleotide linkages at either the 5' or the 3' end. This is the only place that the phosphate backbone modification could occur. Thus, the scope of the claims is not narrowed by the amended language.

Claims 42, 66, and 71 have been objected to because of the language "including at least the following formula". The Office Action indicates that a formula is considered to be a complete structure. Applicants have amended each of these claims to substitute the cited language with the word "comprising". The amendment clarifies the broad scope of the claim and more clearly states that the sequence provided in the claim is the minimum sequence which could be found within a longer sequence.

Claims 42 and 66 have been rejected because of the recitation "increasing the responsiveness" and "enhancing recovery of bone marrow" respectively. The phrases were objected to because no frame of reference was given. Applicants indicate that the frame of reference for each of these parameters is inherent within the language of the claims. For instance, the phrase "increasing the responsiveness" when used in the context of the claim which states "increasing the responsiveness of a cancer cell to a cancer therapy" by administering a CpG containing nucleic acid, it is clear that the claim refers to an increase in effect of the cancer therapy on a cancer cell resulting from the CpG nucleic acid. Thus, the frame of reference is any increase over that which would occur in the absence of the immunostimulatory nucleic acid. Claim 66 teaches that a subject has been exposed to a cancer therapy which damages the bone marrow and the immunostimulatory nucleic acid is administered in an amount which enhances the recovery of the bone marrow. Thus, the frame of reference is that amount of bone marrow recovery which was enhanced as a result of the presence of the immunostimulatory nucleic acid as compared to the amount which would occur

in the absence of the immunostimulatory nucleic acid. The frame of reference of these phrases is found within the language of the claim as a whole.

Rejection of Claims 42-75 Under 35 U.S.C. §112, First Paragraph

Claims 42-75 have been rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is more nearly connected, to make and/or use the invention". The basis for the rejection is that the application does not provide data in any *in vivo* method to effect the conditions mentioned in the claims. Applicants respectfully disagree.

Claims 42-65 relate to methods for increasing the responsiveness of a cancer cell to a cancer therapy. The results of an *in vitro* assay demonstrating this phenomenon are described in the specification on page 24, line 25 - page 25, line 6. In these studies, a B cell lymphoma line WEHI-231 was used to assess the ability of CpG oligonucleotides to rescue a cancer cell from growth arrest. The responsiveness of a cancer cell to a cancer therapy can be increased by maintaining the cell in the cell cycle. It was found that CpG containing oligonucleotides caused these cells to enter and stay in the cell cycle. Tumor cells, like WEHI-231, are able to resist cancer therapy by stopping cellular division. By keeping the cells in the cell cycle, CpG oligonucleotides increase the susceptibility of the cancer cell to a cancer therapy, since cancer therapies recognize rapidly dividing cells and kill them.

Claims 66-70 relate to methods for enhancing recovery of bone marrow by administering to a subject undergoing or having undergone cancer therapy a CpG containing nucleic acid. The specification teaches on page 53, lines 5-10, that "an immunostimulatory oligonucleotide can be administered prior to, along with or after administration of a chemotherapy or immunotherapy to increase the responsiveness of the malignant cells to subsequent chemotherapy or immunotherapy or to speed the recovery of the bone marrow through induction of restorative cytokines such as GM-CSF". The specification on page 30 and page 32 describe the results of *in vitro* assays assessing cytokine production by human cells (PBMC) in

response to CpG nucleic acids. The data is shown in Tables 5 and 7. CpG nucleic acids were able to induce GM-CSF production in these cells. PCT published patent application no. WO 99/58118 describe *in vitro* and *in vivo* studies measuring the ability of CpG nucleic acids to induce hematopoiesis. (A copy of this PCT is enclosed as Exhibit I.) Example 1 describes several studies which demonstrate that CpG induces hematopoietic activity *in vivo* in mice (Figures 1-6). Example 1 also describes the effect of CpG nucleic acids on hematopoiesis *in vivo* following radiation treatment. As is taught by the Example on page 57, lines 15-16, "hematopoietic progenitor cells are considered rather radioresistant". It is concluded on page 58, lines 4-6, that "CpG-ODN compensate radiation induced damage of the lypho-hematopoietic system by accellerating regeneration from hematopoietic progenitor cells". Page 60, lines 15-17 teach "our data indicate that CpG-ODN can mitigate radiation induced myelosuppression via augmentation of hematopoiesis yielding in accelerated reconstitution of the immune system". Example 2 describes *in vivo* assays assessing the effect of CpG nucleic acids on mice treated with another cancer therapy, 5-fluorouracil (5-FU). The results shown in Figure 8 demonstrate that "spleens from animals treated 5-FU plus CpG-ODN weighed more on days 4 and 10 following 5-FU treatment than did spleens from animals receiving with 5-FU alone" (page 61, lines 21-22). The importance of the increased spleen weight in mice is elaborated on page 55, lines 10-11, where it is taught that "in contrast to humans, mice display a basel hematopoietic activity in the spleen". These *in vivo* results clearly demonstrate that CpG enhances the recovery of bone marrow cells (hematopoietic cells) *in vivo*.

Claims 71-75 and new claim 98 relate to methods for improving ADCC in a subject having cancer by administering a CpG containing nucleic acid. ADCC (antibody dependent cellular cytotoxicity) is a process in which an antibody specific for a tumor cell surface antigen, when contacted with a tumor cell results in the specific killing of that tumor cell. The invention involves the finding that CpG nucleic acids enhance ADCC. Support for the teaching that CpG is useful for enhancing ADCC is found in the instant specification (at least on page 53) and at least in parent patent application serial nos. 08/960,774 (filed October 30, 1997) and serial no. 08/738,652 (filed October 30, 1996). Applicants include herewith a copy of the literature

reference by Wooldridge et al. (which includes co-inventors Arthur M. Krieg and George J. Weiner as co-authors) as Exhibit 2. Wooldridge et al. was previously cited to the Patent Office in the instant patent application as reference C22 of the 1449 filed on November 5, 1999. Wooldridge et al. describes *in vivo* studies in which the effect of CpG nucleic acids was examined on ADCC of a lymphoma bearing animal. Figures 3, 4, and 5 (pages 2996-7) demonstrate the dramatic improvement in animal survival when a combination of CpG and antibody was administered compared to antibody alone. In fact, there was a synergistic increase in survival of the animals.

Rejections of Claim 1

Several rejections of claim 1 have been raised. Applicants have cancelled claim 1. Claim 1 was only maintained in the case in order to have one claim pending at the time the divisional was filed. Applicants do not intend to pursue this claim in the above-identified patent application. Therefore, the rejections raised in the Office Action are not addressed with respect to claim 1.

Respectfully Submitted,

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